Clinical Outcome and Failure Risk Comparison between the Use of Autograft and Allograft Tissue in ACL Reconstruction Surgeries

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Abstract

Background: The use of both autograft as well as allograft tissue in anterior cruciate ligament reconstruction surgeries, performed by present day surgeons in patients of a wide age range, is prevalent. However, failure risks in such surgeries depend on a multitude of factors. In order to appropriately use the more suitable type of tissue in patients of ACL reconstruction surgeries, some of the main factors affecting failure risks are investigated. **Procedures:** Extensive data regarding ACL reconstruction surgery patients was collected through MOON (Multi-Center Orthopedic Outcomes Network) patient questionnaires and surgeon forms. The data processing was completed in three parts. In the first part, the occurrence of re-tear in ACL reconstruction patients with allografts vs. those with autografts was determined as a binary outcome (tear/no tear). In addition, a logistic regression was done on any patient-associated factors that are related to incidence of re-tear. The second part of the study was focused on the evaluation of a dependent variable defined as "time to re-tear" in allograft ACL reconstructions, and investigating, using a Cox regression, its link to factors such as gender, age, and graft preparation criteria. Finally, the last part of the study is part of a survival analysis comparison between the time to re-tear of allografts and autografts (failure rates) in terms of the implications of factors such as the Marx score, gender and age. **Outcome:** Firstly**,** allograft reconstructions were 3.242 times more likely to re-tear than autografts and the factors of age and graft type (auto/allo) significantly contributed to incidence of re-tear. Secondly, graft preparation factors showed no significant effect on the time to re-tear of allograft ACL reconstructions. Finally, in the third part of the study, the relative risk of re-tear in allograft reconstructions is 2.283 times higher than autograft ones with age affecting relative re-tear risk, while failure rates (times to re-tear) were similar between the two grafts. **Conclusion:** Generally, allografts have a higher risk of re-tear than autografts. In addition to that, age is a significant factor in affecting risk of re-tear.

INTRODUCTION:

Anterior Cruciate Ligament reconstructions are common orthopedic surgeries in the young, athletic as well as older populations. Thousands of such surgeries are performed each year, with the majority of the surgeries completed with autograft tissue as opposed to allograft tissue. That is in part due to the fact that autogenous bone-patellar tendon-bone (BPTB) graft and the clinical results associated with it have been and remain to be the gold standard (S.K.Y. Chang et al, 2003).

However, the use of allografts as an alternative to autografts in ACL reconstruction has been on the rise over the past few years. That is to overcome the problem of unavailability of patellar tendon autograft due to poor tissue quality (Schwartz et al, 2006) and the limited availability of autograft tissue to the width of the native patellar tendon (in BPTB grafts). There are also multiple potential complications associated with autografts that include patient donor site morbidity or patellofemoral arthrosis mentioned by Dr. Chang, et al. in a study by the University of Hawaii Orthopaedic Residency Program.

The main concern when conducting ACL reconstructions surgeries is the failure risks associated with the type of graft used. So far, there have been virtually no studies that directly compare the failure risks associated with autografts to those of allografts. However, a preliminary unpublished study done by the MOON group on 291 subjects the compared the risk of retear of allografts to that of autografts and found that patients who had an allograft reconstruction were 4.7 times more likely to retear than those who had autografts. The reason behind the presumed higher failure risks of allograft use is not quite known yet and could be affected by a multitude of factors. Such factors may be patient related such as age, gender or

Marx score or they could be donor tissue related, specifically in the way the tissue was prepared by the tissue banks. It was found that age was a contributing factor to re-tear in the model created but Marx scores were not. However, a conjecture relating Marx scores and age is drawn, yet not tested. Also, surprisingly and against reports on tearing native ACLs, it was found that gender was not a factor related to retear risk.

Age of the patient undergoing surgery is often directly correlated with the activity level of the patient, hereby potentially influencing the probability of graft failure after surgeries. Higher graft failure risks have been shown to be more common in the younger / more active population in a study by the MOON group in 2007 in the unpublished study where it was determined that the younger patient had a 1.93 times higher risk of retear than a patient ten years older. However, such correlations do not simply imply causation and the relationship between the variables must be further proven. Knowing the relationship between the use of allografts and failure risks in certain age groups could be very useful when determining the graft type to be used in that age group. It is found that even though odds of retear are higher for allografts regardless of age, the model created showed an overall lower risk of retear for an older patient with an allograft.

The other category of factors potentially affecting allograft failure incidences is the tissue preparation specifics that may vary from one donor tissue bank to another. Valuable knowledge attained by examining the relationship between the preparation techniques and the failure risk of allografts could be used in deciding what type of tissue preparation from which donor bank will be best associated with high clinical success. This success would be demonstrated in the form of lower incidences and risk of re-tear. Disinfection or cleansing of the donor tissue using patented techniques such as Allowash is a preparation process aimed to eliminate any microbial presence

on the tissue surface. It may be possible that such cleansing may have an effect on the biomechanics of the tissue and therefore ultimately an effect on its risk of failure; so such a factor is worth investigating. According to a study by Dr David Jones at the Mayo Clinic College of Medicine, the mechanical properties (tensile strength, cyclic creep) of allograft tissues treated with chemical disinfection are similar to the controls in the experiment that were untreated (Jones et al. 2007). This leads to the incumbent question of whether chemical treatment may affect the tissue post-implantation; in clinical cases. Therefore, the variable of chemical disinfection should be investigated in correlation with risk of retear.

In addition to disinfection by chemicals, tissue banks commonly use gamma irradiation to sterilize the entire tissue as opposed to the surface only. A widely accepted dose of 2.5 Mrad or radiation is thought to have bactericidal and virucidal properties but significantly alters the initial biomechanical properties of soft tissue allograft (Rihn, Jeffrey A. et al, 2005). Such effects make no difference in clinical outcomes (incidences of retear) of surgeries as one study by Jeffrey A. Rihn at the University of Pittsburg School of Medicine shows, but are shown to possibly contribute to allograft failures in another study by Andrew R. Curran et al. that shows graft mechanical alteration in the form of cyclic elongation of the graft, associated with irradiation, that lowers the failure load for the tissue tested. (Curran at al. 2004) A possibility in the discrepancy between the studies could be that Rihn's study was done one 102 patients (39 of which had allografts), a sample size too small to extrapolate results based on. Also, Curran's study was not a clinical test of failure rates but a mechanical testing of the graft after treatment which may or may not have an effect on the clinical outcome of the surgery. As such, it is imperative that the factor of irradiation be considered in the model of factors affecting clinical outcomes of ACL reconstructions.

The purpose of this study is threefold. Firstly, a logistic regression was used to compare autografts to allografts in the incidence of failures as a binary outcome (retear / no-retear) and the effect of patient related characteristics, such as age, potentially associated with graft failures investigated. Secondly, the potential effect of allograft preparation techniques on the allograft failure risks is investigated through a survival analysis model. Finally, the survival analysis will also be used in the third part which attempts to compare relative retear risks of allografts to those of autografts (times to retear are compared) while evaluating patient related variables in the model.

The reason behind the central investigation is to attempt to provide enough knowledge for a surgeon to make a well-measured and justified choice of graft in an ACL reconstruction that would be most appropriate and well-suited to the demographic of a patient.

PROCEDURE

First, a comparison of the incidence of ACL reconstruction failures between the two types of graft was conducted through the statistical analysis of data collected by the MOON (Multicenter Orthopaedic Outcome Network) group of all subjects who underwent ACL reconstruction. The data subject group included patients who had their ACL reconstructions in between the years of 2002 to 2003.

The data collected was in the form of patient surveys that included tests such as the Marx activity scores as well as extensive data relating to the demographic of the patient. There were two surveys collected, a pre-operative patient survey and one post operatively at 2 years from surgery. In addition to that, there were also surgeon surveys that collected detailed information regarding the patient injuries at the time of reconstruction surgery, that included basic data such

as the graft type, source and the extent of injury (on MOON surgeon standardized scales) as well as other potentially relevant findings on the condition of other ligaments in the knee. Following a particular protocol of selection criteria, data obtained from 999 patients was used in the model predicting the incidence of ACL retears and the correlation between the aforementioned dependent variable and a multitude of factors such as graft type, age, gender, and Marx scores that could all potentially influence the outcome of the reconstruction surgery.

The primary outcome was a binary one with the only possibilities of tear or no tear (confirmed in patient phone calls as the incidence of a revision ACL reconstruction after the primary one within the period of 2 years). The factors, age, gender, Marx score and graft type, which may potentially influence the outcome, were each inserted in a logistic regression model using STATA 9.0, an application that performs statistical analyses. However, the correlation between the factors and the outcome was tested one factor at a time to bypass the issue of colinearity of the variables (variable interactions that may affect the outcome), and if found probably significant, was kept in the model. If not, the variable was dropped. Likelihood ratio tests comparing a model with all the variables and a model with the reduced variables were used to finish the model by dropping variables showing a test significance of lower than 0.05. In addition the surgeon performing the surgery was another variable considered and created to account for any 'surgeon effect' variable on the outcome of the reconstruction. The variables' effect on the outcome could then be determined from the resultant model which only had factors that influenced the primary outcome. Statistical calculations on the model were collected.

In the subsequent part of the study, the one investigating graft preparation techniques and other factors and their potential effect on the failure risk of allografts, a survival analysis was done on 200 patients who received allografts. The type of allograft was controlled in all the

patients and was a tibialis allograft. The subjects included in this part of the study were interviewed through phone and patient questionnaires to obtain data such as the incidence of re-tear and time to re-tear. In addition, information including patient demographics (age and gender) as well as graft preparation techniques (use of irradiation or chemical disinfection) corresponding to the allograft used was obtained from the donor tissue banks that provided the graft. These risk factors potentially related to time of re-tear of allograft (determined by patient interviews/questionnaires) were tested via the survival analysis, specifically a Cox regression. Much like in the first model, the variables related to graft preparation (Chemical treatment, irradiation) and those patient-related (age) were tested one at a time to determine any significant effect on the time to failure. The variables showing significance were used to perform another likelihood ratio test which provided an improved model with no variables that had lower significance than 0.05. Statistical data was collected on the variables and the model.

Similarly, the final primary outcome in this study, time to re-tear of graft between autografts and allografts, was investigated using the survival analysis method of Cox regression models. Data was collected from patients in the same year range (2002-2003) whose graft (allograft or autograft) failed. The data collected was both patient and surgeon (surgery) related through the same questionnaires and survey method previously used; and all variables that may potentially have an impact on the primary outcome were tested in a similar model format to the one used in the previous part of the study. Again, statistically relevant data was collected on the variables and their correlation with the primary outcome.

RESULTS

The patient demographic data surveyed and collected was tabulated in table 1. Averages and deviations were calculated on certain demographic data and included in table 2. The logistic regression model constructed included all the variables from tables 1 and 2 and tested the effect of each variable on the outcome of surgery (odds of re-tear) through a Likelihood Ratio (LR) test which compared a model with all the variables included towards the outcome with the model that had reduced variables. The outcome was that graft type and age were the significant factors influencing incidences of re-tear yet, there was no significant interaction between the type of graft used and age. Also none of the variables tested, were found to significantly influence the model constructed. Table 3 contains all the odds ratios for variables predicting re-tear while controlling for the 'surgeon effect'. The odds of re-tear are 3.242 times higher for a patient with an allograft reconstruction with control of age and the surgeon effect. (Without control of surgeon effect the number rises to 3.730) In addition to that, for a subject ten years younger, the risk of re-tear is 2.253 times higher, meaning that statistically speaking, age is a significant predictor of re-tear in ACL reconstruction regardless of graft type. For the age variable correlation, the surgeon effect variable had no impact unlike the graft type.

Further evaluation of the model was performed through a construction of an ROC graph (Receiver-operating characteristic) where the area under the curve was greater than 0.7 at 0.7287 (Figure 1.), meaning that the model's prediction of re-tear based on the variables in the model is adequate.

The second phase of analyses which revolved around investigating factors that lead to allograft re-tear included 359 patients who underwent allograft based ACL reconstructions and

subsequently either re-tore or did not tear the graft. The factors, tissue treatment variables, tested were the use of Allowash and the use of gamma irradiation. Using a Kaplan Meier survival analysis, the tissue treatment factors were not found to have any significant influence on the clinic failure rate of the allograft; since the survival curve is always higher than 0.75 making it difficult to find any correlation between tissue treatment and re-tear risk insignificant.

Concerning the final portion of the study which investigated relative time to re-tear (clinical failure) between allograft based ACL reconstructions and autograft based ones, a cox regression was performed on 38 patients who re-tore their graft in a group of 990 patients who had ACL reconstructions. Like in the first part, different variables (age and graft type) were tested in the model while accounting for the surgeon variable. The outcome was a higher relative risk of re-tear for a patient with an allograft by 2.283 times than a patient with an autograft at a constant age. Moreover, a subject 10 years younger than another had a relative risk 2.410 times higher than the latter regardless of graft type. Both hazard ratios account for the surgeon effect and are tabulated in table 4, along with the ratios with before accounting for the effect. Similarly to the first part results, the surgeon effect does not influence the hazard ratio of the age variable and when accounted for, decreases the hazard ratio for the graft variable. The overall model was deemed plausible by testing Cox-Snell residuals.

Additionally, the mean time to graft failure was calculated and tabulated in table 5, to show that the mean times for autografts and allografts to retear were similar. This means that the rates of retear for both were shown to be similar.

Table 1. Patient Demographic Distribution

Gender	Male	Female
	568, 57%	431, 43%
Type of Graft	Autograft	Allograft
	739, 74%	260, 26%
Tear	No tear	Tear
	952, 95%	47, 5%
Primary or Revision	Primary	Revision
	898, 90%	101, 10%

Table 2. Averages for Demographic Data

	Mean	sd
Age (Years)	26.82	10.8
Height (in.)	68.56	5.08
Weight (lbs)	173.47	42.36
Marx (points)	11.07	5.33

Table 3. Variable risk ratio for re-tear

Variable	Odds/Risk ratio	Odds/Risk ratio (Not accounting for Surgeon Effect)
Graft Type (Allo)	3.242	3.73
Age (10 year increments)	0.922	0.922

Table 4. Variable hazard ratio for relative risk to retear

Variable	Hazard ratio	Hazard ratio (Not accounting for Surgeon Effect)
Graft (Allograft)	2.283	2.788
Age (10 year increments)	0.916	0.916

Table 5. Average time to graft failure

	Average time to retear	Standard Deviation	Number of Subjects
Autograft	12.57	5.57	23
Allograft	13.13	6.55	15

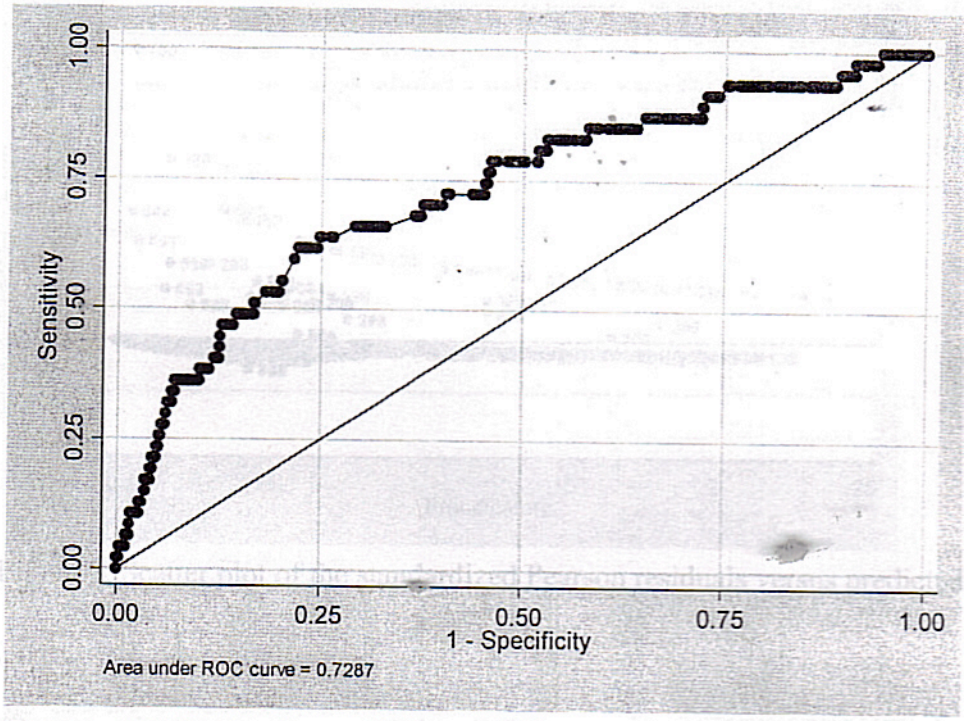

Figure 1. ROC curve for prediction of ACL retear.

DISCUSSION

The statistical analyses done on the cohorts of patients surveyed by the MOON group lead to a few statistically significant conclusions about variables affecting the outcome of an ACL reconstruction surgery.

Firstly, the type of graft used affected both the incidence of re-tear and the odds of re-tear to time. Allografts were 3.242 times more likely to re-tear than autografts and had a higher relative risk of re-tear by a factor of 2.283. Secondly, the age variable proved to influence the incidence of re-tear as well as the relative risk of re-tear. Subjects younger by ten years were 2.253 times more likely to re-tear and had a relative risk of re-tear 2.410 times higher than those ten years older. Although this significant correlation may mean that age affects the clinical outcome of ACL reconstructions, we hypothesize that age and activity levels are related which

maybe the reason that age is an important factor for the trend in outcomes but there are insufficient studies that investigate this correlation in the literature. In addition to age exhibiting a correlation with clinical outcome, Marx scores were also tested but found insignificant, yet we also hypothesize that age and Marx scores may be related. This relationship was not tested, and Marx scores did not provide any additional information.

Tissue preparation techniques in the form of chemical treatment such as allowash were found to be insignificant predictors of failure in allograft ACL reconstructions. This means that clinically, the chemically treated graft performs as well as the non-treated graft. The conclusion seems to concur with the conclusions in the Mayo Clinic study that indicate that chemically treated tissue mechanics are not altered by the chemical treatment.

Our study also showed no significance in gamma irradiation techniques that sterilize tissue in predicting re-tear. The interpretation is that clinically, failure risks are not significantly different for allograft tissue that is irradiated as opposed to non-irradiated. The findings seem to contradict the study by Curran which showed adverse effects of irradiation on the mechanical properties of the issue pre-operatively, yet, it is evident in our and Rihn's study, that clinical failure risks are no different than in untreated tissue. Further studies linking the correlation of mechanical properties of the tissue (failure loads) with clinical failures would be very helpful in reaching further conclusions.

Additionally, the rates of retear for autografts and allografts (based on time to retear) were similar. This comes contrary to studies that have shown allografts to take a longer period of time to biologically incorporate than autograft tissue, leading to an expectation of larger failure rates for allografts in clinical cases. Such a study is done by the Southern California Center for

Sports Medicine showing that autografts demonstrate a more "robust" response of incorporation six months post-operatively linked with increased strength to failure values (Tension mechanically applied before tear of graft). (Jackson et al., 1993). However this study is done in goats, not humans, and the incorporation rate is only linked to mechanical testing results and not clinical failure risks. A study linking human ACL reconstruction failure risks and incorporation rate is not available but would contribute significantly to the conclusions reached.

Although the statistical conclusions based on strong correlations point to autografts being a 'safer' choice between the two grafts in promoting a lower risk of re-tear, the data set of patients that re-tore their ACL graft may have been too small to provide a strong and comprehensive investigation. In addition, the subset of patients that were considered old in age was small in the data population used and may not be sufficient to powerfully extrapolate and generalize trends in a bigger population from a statistical viewpoint. Moreover, it would be worthwhile investigating other allograft preparation techniques such as storage (freeze dried/fresh frozen) that may potentially affect the clinical success rate associated with the allograft used.

Nonetheless, the deduced statistical linkage between variables affecting clinical outcomes of ACL reconstructions serves as a reference of caution for surgeons deciding between allograft or autograft use in routine ACL surgeries, especially in younger populations who are at a statistically higher risk of ACL graft re-tear.

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